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Neutrophil function in pregnancy

Background:

Pregnancy is an immunological challenge for mother and fetus, and the establishment of immune tolerance at the fetal-maternal interface is essential. The semi-allogeneic setting of trophoblast invasion and decidua development is highly regulated and accompanied by leukocyte infiltration. Innate and adaptive leukocyte accumulation and localization within the placenta is highly organized to maintain normal development. Especially the function and phenotype of macrophages has been well described (1, 2). However other leukocyte populations have been identified to play a crucial role in placenta homeostasis, including neutrophils, cytotoxic and regulatory T-cells. Neutrophils form an essential part of the innate immune responses and are the first inflammatory cells migrating towards acute infections. Their role in regulating adaptive immunity is less well understood but has been described in the setting of cancer (3, 4). Further, neutrophils have been implicated in the establishment of maternal tolerance through the induction of regulatory T-cells and neutrophil depletion led to abnormal development of the fetal-maternal unit in mouse models (5). Imbalance of leukocyte infiltration and localization within the placenta has been linked to complications in pregnancy, including gestational diabetes mellitus, preeclampsia and preterm labor, however a detailed picture of leukocyte dysfunction is missing.

Hypothesis and Objectives:

We hypothesize that innate and adaptive leukocyte infiltration, function and localization within the placenta is altered in health and disease and that immune cell interactions play a crucial role in maintaining immune tolerance at the fetal-maternal interface.

The purpose of this study is to evaluate leukocyte composition and localization within the placenta in health and disease including innate (neutrophils, monocytes, macrophages, innate lymphoid cells) and adaptive (CD8, CD4 T-cell, B-cell subsets) immune cells. Further, we will evaluate neutrophil function and focus on lymphocyte/neutrophil, trophoblast/neutrophil and macrophage/neutrophil interactions.

Methodology:

The PhD candidate will comprehensively characterize the immune landscape in healthy and diseased placenta tissue samples using multicolor flow cytometry (18-plex), next-generation sequencing and multiplex fluorescence microscopy (3, 6). Functional analysis of neutrophils will be investigated in assays of shape change, chemotaxis and Ca^{2+} signaling and levels of neutrophil specific enzymes will be assessed by ELISA and western blots. Lymphocyte/neutrophil, trophoblast/neutrophil and macrophage/neutrophil interactions will be studied using in vitro co-culture systems. In this study, we will make use of established cell culture models, primary cells and tissue from consented patients.

References:

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